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| 10/026,992      | 12/19/2001  | David Bebbington     | VPI/00-130-4        | 2621             |

7590 08/30/2005  
Tina Powers  
VERTEX PHARMACEUTICALS INC.  
130 Waverly Street  
Cambridge, MA 02139-4242

EXAMINER

RAO, DEEPAK R

|          |              |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

1624

DATE MAILED: 08/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/026,992

Applicant(s)

BEBBINGTON ET AL.

Examiner

Deepak Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 16, 2005 has been entered.

Claims 1-27 are pending in this application.

### ***Withdrawn Rejections/Objections:***

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

### ***The following rejections are maintained:***

Claims 11-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of colon cancer, does not reasonably provide enablement for the treatment of all other diseases embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

The amendment to the claims and applicant's arguments have been fully considered but they were not deemed to be sufficient. Applicant relies on the amendment to claim 21 wherein "Alzheimer's disease" is deleted, to overcome the rejection. This is not, however, deemed to be sufficient as the claims continue to contain all types of diseases that are mediated by Aurora-2 (claim 14) or GSK-3 (claim 20) including many of the diseases specifically recited in the other claims, for which there is no sufficient enablement in the specification as filed. Further, claim 20 includes 'a method of treating Alzheimer's disease' because the specification provides that it falls within the meaning of 'GSK-3-mediated disease', see page 18, lines 4-12.

The reasons provided in the previous office action are depicted below for convenience:

The instant claims are drawn to 'a method for inhibiting Aurora-2 kinase; GSK-3; Src; etc. activity' and 'a method of treating diseases mediated by Aurora-2, GSK-3, etc.' which according to specification is drawn to a therapeutic use, e.g., in treating different cancers, Alzheimer's disease, multiple sclerosis, etc. (see pages 17-21). First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assays and procedures are provided in the specification pages 311-320 related to aurora-2 kinase, GSK-3, Src inhibition, wherein the inhibitory activity data ( $K_i$ ) for some of the compounds of the invention is provided, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the disorders of the instant claims. The disorders encompassed by the instant claims include proliferative disorders or cancers, which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical

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art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. "How sister kinetochores attach to microtubules from opposite spindle poles during mitosis (bi-orientation) remains poorly understood", see Tanaka et al. (PubMed Abstract enclosed). Also, Rogers et al., express that "How the selective release of chromosome cohesion is regulated during meiosis remains unclear". This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

A 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Further, neurodegenerative diseases covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that 'some degenerative diseases are difficult to classify because they involve multiple anatomic locations' (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that '[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease' (pg. 1994).

Further, the list of the diseases includes multiple sclerosis, which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova et al. (PubMed Abstract enclosed) state that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not

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clearly understood”, see the abstract. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant’s attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that ‘a claimed invention must have a specific and substantial utility’. The disclosure in the instant case is not sufficient to enable the instantly claimed ‘treating of a Aurora-2 mediated disease’ solely based on the inhibitory activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as “sufficient working examples”, “the level of skill in the art” and “predictability”, etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

### ***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al., WO 00/39101 or Armistead et al., WO 01/60816 or Pease et al., WO 01/64655.

The references individually teach substituted pyrimidinyl compounds having kinase inhibitory activity:

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See WO 00/39101, formula I in page 2 and the species of the Example 135; WO 01/60816, compounds 1, 5-8, 33-35, etc.; and WO 0164655, compound 119. The compounds are taught to be useful as kinase inhibitors useful as pharmaceutical therapeutic agents, see the disclosure in each of the references.

The instant claims recite that  $R^y$  is  $T-R^8$  wherein  $R^8$  is halo,  $C_{1-6}$  aliphatic (e.g., methyl) etc., as compared to the reference compounds which are unsubstituted at the analogous position (i.e., substituted with hydrogen).

The references however, teach a substituent at the adjacent 5-position, and therefore, the instant claims differ from the reference compounds by having a substituent at a position different from the reference compounds. Therefore, the instant claims include compounds that are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds, i.e., as pharmaceutical agents. It has been held that a compound, which is structurally isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950); *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Alternatively, the instantly claimed compounds differ from the reference compounds by a  $-CH_2$  group (H vs.  $CH_3$ ) and it is well established that compounds that differ by a  $-CH_2$  group

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are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Acting-SPE of 1624, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR



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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read "Deepak Rao", with a stylized flourish at the end.

**Deepak Rao**  
**Primary Examiner**  
**Art Unit 1624**

August 22, 2005